RFP- BAA-NIH-BARDA-NIAID-DMID-2007003
Amendment No. 1 (Questions & Answers)

This Amendment provides questions submitted by potential offerors and the responses provided by the NIAID. The responses are offered for information only and do not modify or become part of this solicitation. This Amendment may be updated to add any further questions and their related responses. All potential offerors are advised to refer back to this Amendment for additional Q&A. No questions will be accepted after December 8, 2007.

"Advanced Development of Multivalent Filovirus (Ebola and Marburg) Hemorrhagic Fever Vaccines"

Amendment No.:	1 (1st Posting)
Amendment Issue Date:	November 7, 2007 (Questions 1 through 9)
Proposal Due Date/Time:	December 18, 2007, 3:00 pm EST (UNCHANGED)
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Offerors must acknowledge receipt of the final posting of Amendment #1, on each copy of the proposal submitted. Failure to receive your acknowledgment of this Amendment may result in the rejection of your proposal.

The hour and date specified for receipt of proposals HAS NOT been extended.

THE FOLLOWING PAGES PROVIDE ANSWERS CONCERNING A NUMBER OF INQUIRIES WE HAVE RECEIVED FOR THE ABOVE NUMBERED SOLICITATION:

Question 1 In Attachment 5 of the BAA, the NIAID indicates that "non-clinical studies must be conducted in compliance with the U.S. Code of Federal Regulations 21 CFR 58 (Good Laboratory Practice for Nonclinical Laboratory Studies)." However, page 4 of 12 of Attachment 6 states, "studies required to be conducted under GLP should be clearly identified." If an offeror proposes to perform proof-of-concept efficacy studies under Good Documentation Practices in a research and development environment, as opposed to a GLP environment, while also performing all safety studies in a GLP environment, would the offeror's technical solution be deemed to be compliant with the requirements of the BAA? If NIAID does require that all non-clinical studies be performed in a GLP environment, can NIAID provide offerors with a list of those entities that can perform non-clinical studies in rodents and non-human primates under GLP conditions at BSL-4?

Proposed proof of concept efficacy studies performed under Good Documentation Practices in a research and development environment are acceptable. Offerors should be aware that some critical efficacy studies to satisfy the requirements established by the "Animal Rule" 21 CFR § 601.90-95 will require GLP studies. Efficacy studies in the base period should be designed and conducted in a manner to facilitate GLP compliance if pivotal animal studies are conducted. Studies to satisfy the requirements established by 21 CFR 58 must be conducted in accordance with GLP.

Question 2 Option 2 requires "the conduct of studies to develop a lyophilized final container formulation to improve vaccine shelf-life and storage temperature." If an offeror proposes an alternative stabilization technology for this option will the offeror's technical approach be deemed compliant with the BAA, or does NIAID specifically require lyophilization?

A lyophilized preparation is the objective of this option. Proposals using alternative technologies will be considered and evaluated using the Technical Evaluation Criteria for Option 2 which are listed in Section M.

Question 3 Option 1 requires "performance of all activities associated with the transfer and scale-up from pilot scale to large-scale cGMP manufacturing and release of 200,000 doses minimum target scale of the candidate vaccine for use in further clinical trials." If an offeror proposes performance of process scale-up, process characterization, pre-validation, and assay validation, in the base years of the contract, rather than delaying all of these activities to the Option year, will the offeror's proposal be deemed compliant with the BAA? Is there a possibility that delaying these activities to the Option years would prohibit completion of all of these activities and manufacture of the 200,000 doses in two years?

Decisions to exercise options will be based on the data generated in the base period. When appropriate data are available the government will consider exercising the options.

Question 4 In the BAA on page 3 of Attachment 4, NIAID has articulated its requirement for a vaccine that yields immunity to three (3) strains of Ebola virus and two (2) strains of Marburg virus. This requirement is stated as follows:

"The ultimate goal of the program is development through a Phase 1 clinical trial, of a multivalent vaccine that protects against ZEBOV, SEBOV, ICEBOV, RAVN, and at least one other strain of Marburg."

However, in Attachment 5, page 2, paragraph D, the text reads:

"The target multivalent vaccine must **contain/express antigens** of SEBOV, ZEBOV, ICEBOV, RAVN, and either Ci67, Musoke, or another closely related strain of Marburg, and must provide for a relatively rapid onset of protection following no more than two doses; post exposure prophylaxis will also be considered."

Is the ultimate goal of NIAID and its collaborating agencies the development of a vaccine that protects against the five (5) named strains of virus, or is that goal a vaccine that contains antigens for all five (5) strains?

In other words, if, because of cross-immunity, it is possible to develop products that provide protection from all five (5) strains and if this protection might be provided with fewer than five (5) antigens, would that fulfill the BAA's requirement?

The ultimate goal is a safe and efficacious vaccine that would protect against human Ebola and Marburg infections. Proposals that describe product development plans for multivalent vaccines that protect against ZEBOV, SEBOV, ICEBOV, RAVN, and at least one other strain of Marburg will be considered. One approach is to include an individual antigen for each virus. Alternative approaches will be considered. Appropriate data and justification should be provided to support an alternate approach.

Question 5 Regarding the language under Attachment 5 page 3, item 2) Technical Requirements (Base Period), Item B:

"Non-clinical studies must be conducted in compliance with the US Code of Federal Regulations 21 CFR 58 (Good Laboratory Practice for Nonclinical Laboratory Studies)."

It is known that BSL4 laboratories do not now adhere to GLP standards. While conditions at a BSL4 laboratory might approximate GLP, they would not conform exactly. In light of this situation, would you please clarify the requirement for adherence to GLP?

Following from the matter introduced in the previous paragraph: Which nonclinical studies are at issue? Efficacy/Safety? Toxicity? Correlates of immunity?

Proposed proof of concept efficacy studies performed in a research and development environment are acceptable. Offerors should be aware that some critical efficacy studies to satisfy the requirements established by the "Animal Rule" 21 CFR § 601.90-95 will require GLP studies. Efficacy studies in the base period should be designed and conducted in a manner to facilitate GLP compliance if pivotal animal studies are conducted. Studies to satisfy the requirements established by 21 CFR 58 must be conducted in accordance with GLP.

Question 6 Does the NIAID (and/or other funders that issued this BAA) plan to underwrite the required pivotal animal efficacy studies with contract funding? Please clarify this relative to Attachment 6 Page 2, Section 3, A. Item 1, which reads:

"A copy of the comprehensive, overall development plan that is currently being followed to develop the vaccine. This should include all activities up through licensure under the 'Animal Rule,' including Phase 3 clinical trials, consistency lot manufacturing, and pivotal animal studies. A Gantt chart format with acceptable predecessor/successor links is acceptable."

Is the BAA requiring a description of the overall development plan—knowing that pivotal animal efficacy studies would not be undertaken —or that the plan should be written with the understanding that the NIAID will fund the pivotal animal efficacy studies?

Which portions of this development plan will NIAID be funding? Are NIAID *et al.* asking the contractors to report what they would do, were they to secure full funding for all elements in the overall development plan question? Or are NIAID and its partner agencies asking contractors to bear the cost of any unfunded elements?

Offerors are asked to provide the product development plan for the vaccine they are proposing. Include all aspects that indicate how the offeror envisions the progression of the vaccine from its current status through licensure. The product development plan through licensure is requested to enable Offerors to demonstrate the feasibility of their proposed licensure path.

This solicitation will fund the manufacture of clinical grade material, conduct of nonclinical studies, development of an IND, and conduct of a Phase 1 clinical trial in the base period. Options, if exercised, include large scale manufacture of the candidate vaccine, development of a lyophilized formulation, and conduct of a phase 2 clinical trial.

Future solicitations will be based on Government needs and the availability of funding. The government is not asking offerors to commit funding to any additional work beyond the scope of this solicitation.

Question 7 For pivotal efficacy studies, must all animals be challenged by aerosol? Does the BAA stipulate the routes of challenge? Does the BAA assume parenteral challenges will occur? Aerosol? Both?

Challenge routes should be proposed and justified by the offeror.

Question 8 In Attachment 5, page 1, Research Objectives, Scope, **t**here is a note about development of adjuvants in the section describing activities NOT supported. Would the potential use of an adjuvant not yet FDA licensed disqualify the project from funding?

Candidate vaccines formulated with adjuvants other than those currently approved by the US FDA for use in humans will be considered.

Question 9 On page 1 of Attachment 5, it is indicated that "the development of new animal models or refinement of existing animal models" will not be supported under this solicitation. However, the BAA requires that Ivory Coast be one of the strains against which the multivalent vaccine protects. The offeror is not aware of a fully developed animal model for Ivory Coast, while animal models are developed and available to the offeror for all other strains required. As such, if an offeror includes in its Statement of Work the development of an animal model for Ivory Coast, would the offeror's technical solution be deemed compliant with the BAA? If NIAID will not allow for the inclusion of development of the Ivory Coast animal model, does NIAID have access to this animal model, and can it be provided to offerors in performance?

We are asking Offerors that have developed a platform technology which has been used successfully to demonstrate the efficacy of their vaccine candidate/s in non-human primate (NHP) Ebola **and** Marburg challenge models to respond to this solicitation.

Challenge studies are not required in this solicitation for the proposed multivalent filovirus vaccine candidates and therefore an animal challenge model for the Ivory Coast virus is not needed at this time. Studies to demonstrate that individual components of the multivalent filovirus vaccine are immunogenic and that there is no immune interference between any of the components in the multivalent final product are required.

Reference is made to Attachment 5 Paragraph 1 (Scope) F. "Offerors must propose a well-defined and feasible Product Development Plan for advancing the multivalent filovirus vaccine candidate by carrying out the following research and development activities as specified in the negotiated Statement of Work", and the following subparagraphs (1-10) for the details requested in the product development plan for this solicitation. This solicitation represents a first step in achieving an ultimate goal of a multivalent filovirus vaccine that offers protection against at least 5 different filoviruses.